REVIEW ARTICLE

Current Therapies and Emerging Drugs in the Pipeline for Type 2 Diabetes

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Background: Diabetes is a global epidemic that affects 347 million people worldwide and 25.8 million adults in the United States. In 2007, the total estimated cost associated with diabetes in the United States in 2007 was $174 billion. In 2009, $16.9 billion was spent on drugs for diabetes. The global sales of diabetes pharmaceuticals totaled $35 billion in 2010, and these are expected to rise to $48 billion by 2015. Despite such considerable expenditures, in 2000 only 36% of patients with type 2 diabetes in the United States achieved glycemic control, defined as hemoglobin A_{1c} <7%.

Objective: To review some of the most important drug classes currently in development for the treatment of type 2 diabetes.

Discussion: Despite the 13 classes of antidiabetes medications currently approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes, the majority of patients with this chronic disease do not achieve appropriate glycemic control with these medications. Many new drug classes currently in development for type 2 diabetes appear promising in early stages of development, and some of them represent novel approaches to treatment, with new mechanisms of action and a low potential for hypoglycemia. Among these promising pharmacotherapies are agents that target the kidney, liver, and pancreas as a significant focus of treatment in type 2 diabetes. These investigational agents may potentially offer new approaches to controlling glucose levels and improve outcomes in patients with diabetes. This article focuses on several new classes, including the sodium-glucose cotransporter-2 inhibitors (which are furthest along in development); 11beta-hydroxysteroid dehydrogenase (some of which are now in phase 2 trials); glycogen phosphorylase inhibitors; glucokinase activators; G protein–coupled receptor 119 agonists; protein tyrosine phosphatase 1B inhibitors; and glucagon-receptor antagonists.

Conclusion: Despite the abundance of FDA-approved therapeutic options for type 2 diabetes, the majority of American patients with diabetes are not achieving appropriate glycemic control. The development of new options with new mechanisms of action may potentially help improve outcomes and reduce the clinical and cost burden of this condition.

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Diabetes is a chronic, progressive disease that affects approximately 347 million people worldwide.[1] In the United States, 25.8 million Americans have diabetes, and another 79 million US adults aged ≥20 years are considered to have prediabetes.[2] Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States. It is a major cause of heart disease and stroke and is the seventh leading cause of death among US adults.[2]

The total estimated cost for diabetes in the United States in 2007 was $174 billion,[2] and between 2007 and

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KEY POINTS

➤ Approximately 25.8 million adult Americans have diabetes. In 2007, diabetes cost the United States an estimated $174 billion, and in 2009, $16.9 billion was spent on antidiabetes medications.

➤ Nevertheless, the majority of American patients with diabetes do not achieve glycemic control with the currently available pharmacotherapies.

➤ Several novel and promising medications are currently in development, targeting the kidney, liver, and pancreas in the treatment of type 2 diabetes.

➤ Many of these investigational agents involve new mechanisms of action that offer new therapeutic targets and may help improve glucose control in patients with diabetes.

➤ The new drug classes in development include the sodium-glucose cotransporter-2 inhibitors (which are furthest along in development); the 11beta-hydroxysteroid dehydrogenase; glycogen phosphorylase inhibitors; glucokinase activators; G protein–coupled receptor 119 agonists; protein tyrosine phosphatase 1B inhibitors; glucagon-receptor antagonists.

➤ Several of these new classes are associated with low potential for hypoglycemia, representing a potentially new approach to diabetes drug therapy.

➤ The development of new options with new mechanisms of action may potentially help improve patient outcomes and reduce the clinical and cost burden of this chronic disease.

2009, the estimated cost attributable to pharmacologic intervention in the treatment of diabetes increased from $12.5 billion to $16.9 billion.[3-5] Global sales for diabetes medications totaled $35 billion in 2010 and could rise to $48 billion by 2015, according to the drug research company IMS Health.[6,7] In 2009, $1.1 billion was spent on diabetes research by the National Institutes of Health.[8] Despite these staggering costs, currently there are still no proved strategies to prevent this disease or its serious complications.

According to the 1999-2000 National Health and Nutrition Examination Survey, only 36% of patients with type 2 diabetes achieve glycemic control—defined as hemoglobin (Hb) A_{1c} <7%—with currently available therapies.[9] Lifestyle modification remains the most important and effective way to treat diabetes; however, the majority of patients with type 2 diabetes are unable to maintain such a rigid lifestyle regimen. For most patients with type 2 diabetes, pharmacologic intervention will therefore be needed to maintain glycemic control.[2]

Tables 1 and 2 list the 13 classes of medication currently approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes. Despite this abundance of pharmacotherapies, new medications with different mechanisms of action or new approaches to therapy are needed to improve patient outcomes and reduce the clinical and cost burden of this serious condition.

Indeed, the number of diabetes medications for type 2 diabetes is expected to grow in the next few years, considering the many promising investigational therapeutic options currently in development that may gain FDA approval in the future. This article reviews some of the therapies that are currently being tested and may soon become new options for the treatment of type 2 diabetes (Table 3).

Sodium-Glucose Cotransporter-2 Inhibitors

The sodium-glucose cotransporter (SGLT)-2 inhibitors are a new investigational drug class for the treatment of type 2 diabetes. These agents work at the kidney through insulin-independent mechanisms and should, therefore, theoretically reduce the risk for weight gain that often plagues some of the current antidiabetes drugs. The kidney contributes to glucose balance by:
• Producing glucose through gluconeogenesis[10]
• Utilizing glucose in the renal medulla[10]
• Reabsorbing up to 100% of the filtered glucose to maintain the normal circulating glucose pool.[11]

Two sodium-dependent glucose transporters—SGLT1 and SGLT2—have been identified as the major transporters of glucose in humans.[12,13] SGLT2 is expressed almost exclusively in the S1 segment of the proximal tubule and accounts for >90% of renal glucose reabsorption. SGLT1 is expressed in the heart, gastrointestinal tract, skeletal muscle, liver, and lung, and in the S3 segment of the proximal tubule, where it accounts for only <10% of filtered glucose reabsorption.[14] SGLT2 is therefore the major transporter responsible for renal glucose reabsorption and is a useful therapeutic target for the treatment of diabetes.

Selective inhibition of this transporter will decrease the reabsorption of filtered glucose, lower plasma glucose concentration, and improve glycemic control. Few studies have indicated that the expression of SGLT2 is up-regulated in diabetes,[15,16] a finding that emphasizes the importance of blocking this pathway to control or decrease plasma glucose. Several SGLT2 inhibitors have been developed and are in various phases of clinical trials.[17]

The most advanced agent in this class is dapagliflozin, which has been tested in phase 3 clinical trials in patients with type 2 diabetes as monotherapy,[18] with metformin[19] or with glimepiride,[20] or in combination

Table 1 FDA-Approved Antidiabetic Agents for the Treatment of Type 2 Diabetes

Class	Drug (brand)	Mechanism of action[a]	HbA$_{1c}$ reduction, %[b]	Effect on weight	Adverse effects[a]	Precautions/Comments
Alpha-glucosidase inhibitors	Acarbose (Precose) Miglitol (Glyset)	Delay complex carbohydrate absorption	0.5-0.8	Weight neutral	Flatulence, diarrhea, abdominal pain	Titrate slowly to minimize gastrointestinal effects
Amylin analog	Pramlintide (Symlin)	Acts in conjunction with insulin to prolong gastric emptying, reduce postprandial glucose secretion, promote appetite suppression	0.5-1	Weight loss	Nausea, vomiting	*Black box warning:* Coadministration with insulin may induce severe hypoglycemia Injectable drug
Biguanide	Metformin (Glucophage)	Decrease hepatic glucose output Increase peripheral glucose uptake	1-2	Weight neutral	Nausea, vomiting, diarrhea, flatulence	Taken with meals Avoid use in patients with renal or hepatic impairment or with CHF, because of increased risk for lactic acidosis
Bile acid sequestrant	Colesevelam (Welchol)	Binds to intestinal bile acids Mechanism of action for diabetes control unknown	0.5	Weight neutral	Constipation, dyspepsia, nausea	
DPP-4 inhibitors	Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta)	Slow inactivation of incretin hormones	0.5-0.8	Weight neutral	Not clinically significant	
Dopamine agonist	Bromocriptine (Parlodel)	Mechanism of action for diabetes control unknown	0.5-0.7	Weight neutral	Nausea, vomiting, dizziness, headache, diarrhea	
Incretin mimetics	Exenatide (Byetta) Liraglutide (Victoza)	Stimulate insulin secretion, slows gastric emptying, suppresses glucagon release, induces satiety	0.5-1	Weight loss	Nausea, vomiting, diarrhea	Acute pancreatitis has been reported during postmarketing experience Injectable drug
Insulin preparations: rapid-, short-, intermediate-, long-acting, premixed	Refer to Table 2	Exogenous insulin	Up to 3.5	Weight gain	Hypoglycemia	
Nonsulfonylurea secretagogues	Nateglinide (Starlix) Repaglinide (Prandin)	Stimulate insulin secretion from the pancreas	1-1.5	Weight gain	Hypoglycemia	Taken with meals to control rapid onset
First-generation sulfonylureas	Chlorpropamide (Diabinese) Tolazamide (Tolinase) Tolbutamide (Orinase)	Stimulate insulin secretion from the pancreas	1-2	Weight gain	Hypoglycemia	Use of these agents has declined in response to adverse effects and unpredictable results
Second-generation sulfonylureas	Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase, Diabeta, Glynase)	Stimulate insulin secretion from the pancreas	1-2	Weight gain	Hypoglycemia	
Thiazolidinediones	Pioglitazone (Actos) Rosiglitazone (Avandia)	Increase peripheral tissue insulin sensitivity	0.5-1.4	Weight gain	Edema	*Black box warning:* These agents can cause or exacerbate CHF Contraindicated in patients with NYHA class III or IV heart failure

[a]Lacy CF, et al, eds. *Drug Information Handbook.* 18th ed. Hudson, OH: Lexi-Comp; 2009-2010.
[b]Nathan DM, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care.* 2006;29:1963-1972.
CHF indicates congestive heart failure; DPP, dipeptidyl peptidase; HbA$_{1c}$, glycated hemoglobin; NYHA, New York Heart Association.

with insulin, and with insulin plus oral antidiabetic agents.[21] Overall, the HbA$_{1c}$-lowering effect of dapagliflozin ranged from 0.35% to 0.90% (change from baseline and placebo subtracted).[18-23]

In addition, dapagliflozin also had beneficial effects on fasting blood glucose, with reductions from baseline of 10 mg/dL to 25 mg/dL,[19,20] as well as postprandial area under the curve, systolic blood pressure (3-6 mm Hg),[22] and body weight (0.46-4.5 kg).[18-23] Small increases in blood urea nitrogen and hematocrit, as well as a higher risk for reversible genitourinary infections, were seen with dapagliflozin.[18-23]

The FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) recently (July 19, 2011) reviewed the global clinical development program database for dapagliflozin and voted 9 to 6 against recommending its approval, citing "fears that the product may cause about a 5-fold increase in breast and bladder cancer."[24] Some EMDAC members did not accept the sponsor's explanation that the increased risk seen in patients taking this drug was preexisting and was likely linked to the study's uneven subject selection process. Although some analysts suggest that an outside panel of experts will still recommend the approval of dapagliflozin, such an

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Table 2 Insulin Preparations

Drug (brand)	Onset time[a]	Peak time[a]	Duration[a]	Comments
Rapid-acting				
Insulin aspart (NovoLog)	10-20 min	1-3 hr	3-5 hr	Administer within 15 min before or immediately after meals
Insulin glulisine (Apidra)	25 min	45-48 min	4-5 hr	
Insulin lispro (Humalog)	15-30 min	0.5-2.5 hr	3-6.5 hr	
Short-acting				
Insulin regular (Novolin R, Humulin R)	30-60 min	1-5 hr	6-10 hr	Administer 30 min before meals
Intermediate-acting				
Insulin NPH (Novolin N, Humulin N)	1-2 hr	6-14 hr	16-24+ hr	Cloudy appearance
Long-acting				
Insulin detemir (Levemir)	1.1-2 hr	3.2-9.3 hr	5.7-24 hr (dose-dependent)	Do not mix with other insulins
Insulin glargine (Lantus)	1.1 hr	None	24 hr	
Premixed				
70% Insulin aspart protamine/30% insulin aspart (NovoLog Mix 70/30)	10-20 min	1-4 hr	24 hr	Cloudy appearance Administer within 15 min before meals
75% Insulin lispro protamine/25% insulin lispro protamine (Humalog Mix 75/25)	15-30 min	2 hr	22 hr	
50% Insulin lispro protamine/50% insulin lispro protamine (Humalog Mix 50/50)	15-30 min	2 hr	22 hr	
70% Insulin NPH/30% insulin regular (Humulin 70/30, Novolin 70/30)	30 min	1.5-12 hr	24 hr	Cloudy appearance Administer within 30 min before meals
50% Insulin NPH/50% insulin regular (Humulin 50/50)	30-60 min	1.5-4.5 hr	7.5-24 hr	

[a]McEvoy GK, ed. *American Society of Health-System Pharmacists Drug Information*. Bethesda, MD; 2008.
NPH indicates neutral protamine Hagedorn.

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approval may come with strong warnings about the drug's potential for risk of malignancy.[25]

Despite the recent setback from the FDA's advisory board, the future for this drug class (ie, SGLT2 inhibitors) is promising. Some 4 clinical trials involving SGLT2 inhibitors are currently recruiting patients. Of all the diabetes drugs in the pipeline, SGLT2 inhibitors will most likely be the next class of drugs to be added to the clinician's armamentarium for the management of patients with type 2 diabetes.

11Beta-Hydroxysteroid Dehydrogenase Type 1 Inhibitors

The 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) inhibitor is an enzyme that converts the inert hormone cortisone to its active form, cortisol, in target tissues.[26] Excess cortisol can cause insulin resistance by inhibiting pancreatic beta-cell insulin secretion and peripheral glucose uptake, and by promoting gluconeogenesis.[27] 11beta-HSD1 is up-regulated in adipose tissues of patients with the metabolic syndrome.[28]

In animal studies, transgenic mice overexpressing 11beta-HSD1 eventually develop glucose intolerance, insulin resistance, dyslipidemia, and hypertension.[29,30]

Because of its specific role in glucocorticoid interconversion, inhibition of this enzyme can decrease glucocorticoid activity and improve the components involved in the metabolic syndrome. Using 11beta-HSD1–knockout animals, researchers have shown that such inhibition can improve insulin sensitivity, reduce body weight, and lower triglyceride levels.[31]

In humans, 11beta-HSD1 inhibitors have been shown to improve lipid profiles, fasting glucose levels,[32] and hepatic insulin sensitivity.[33] The most advanced drug in this class in development is INCB13739.[34] In a double-blind placebo-controlled phase 2b clinical trial, 302 patients with type 2 diabetes (mean HbA$_{1c}$, 8.3%) who had been receiving metformin monotherapy (mean dose, 1.5 g daily) were randomized to receive 1 of 5 doses of INCB13739, or placebo, once daily for 12 weeks.[34]

After 12 weeks, compared with placebo, patients who received 200 mg of INCB13739 demonstrated significantly lower HbA$_{1c}$ (–0.6%), fasting plasma glucose (–24 mg/dL), and homeostasis model assessment–insulin resistance (–24%). A reversible dose-dependent elevation in adrenocorticotrophic hormone, generally within the normal reference range, was also noted. Therapy with INCB13739 did not change basal cortisol homeo-

Table 3	Drugs in the Pipeline for Type 2 Diabetes	
Drug category	Mechanism of action	Comments
Sodium-glucose cotransporter-2 inhibitors	Inhibit reabsorption of glucose at the proximal tubule of the kidney, thereby decreasing systemic hyperglycemia	Low potential for hypoglycemia Furthest along in clinical trials
11beta-hydroxysteroid dehydrogenase type 1 inhibitors	Inhibit an enzyme responsible for activating cortisone to cortisol, which minimizes antiglycemic effects of cortisol	Low potential for hypoglycemia All drugs currently in phase 2 clinical trials
Glycogen phosphorylase inhibitors	Inhibit enzymes responsible for hepatic gluconeogenesis	Still very early in development Oral agents have shown promising results in animals and humans
Glucokinase activators	Activate key enzyme to increase hepatic glucose metabolism	Several drugs are currently in phase 2 clinical trials
G protein–coupled receptor 119 agonists	Mechanisms unknown Activation induces insulin release and increases secretion of glucagon-like peptide 1 and gastric inhibitory peptide	Still very early in development Animal data are available
Protein tyrosine phosphatase 1B inhibitors	Increase leptin and insulin release	Still very early in development A potential weight-loss medication
Glucagon-receptor antagonists	Block glucagon from binding to hepatic receptors, thereby decreasing gluconeogenesis	Low potential for hypoglycemia

stasis, testosterone levels in men, and the free androgen index in women. Adverse events were similar across all treatment groups.[34]

The 11beta-HSD1 is an interesting drug class that is still in very early stages of development. Available data so far strongly suggest that 11beta-HSD1 inhibitors are potential options for the treatment of type 2 diabetes, although additional clinical testing is needed.[35] No drug in this class has entered phase 3 clinical trials.

Glycogen Phosphorylase Inhibitors

The liver is central to glucose handling and homeostasis. It accounts for approximately 90% of the body's endogenous glucose production. In patients with type 2 diabetes, excessive hepatic glucose production, along with insulin resistance, can contribute to hyperglycemia. Hepatic glucose production has 2 major pathways—glycogenolysis and gluconeogenesis. Inhibition of hepatic glucose production has become the focus of newer antidiabetic agents for the treatment of type 2 diabetes.[36]

One specific target is glycogen phosphorylase, which catalyzes the phosphorolytic cleavage of glycogen to produce glucose-1-phosphate, which is then isomerized by phosphoglucomutase to glucose-6-phosphate and then enters the glycolytic pathway to produce glucose.[36] Creating an inhibitor that specifically targets glycogen phosphorylase would then essentially decrease the amount of glucose produced by the liver.

There are 5 binding sites on the glycogen phosphorylase enzyme that have been found to be potential targets—the catalytic site, inhibitor site, adenosine monophosphate (AMP) allosteric site, glycogen storage site, and a new allosteric binding site.[37] Findings from a study by Martin and colleagues show that CP-91149 is a glycogen phosphorylase inhibitor that binds to the inhibitor site and reduces plasma glucose levels in mice.[38]

Martin and colleagues found that oral CP-91149 indirectly inhibits gluconeogenesis via the disruption of glucose/glycogen cycling and inhibits the human liver glycogen phosphorylase a enzyme, thereby improving glucose levels. In addition, CP-91149, which has been characterized in vitro and in vivo, suppressed glycogenolysis in both rat and human liver cells.[38] When studying obese mice, the investigators found that a single 50-mg/kg oral dose of CP-91149 reduced plasma glucose concentrations to near-normal levels 3 hours after administration (plasma glucose, 235 ± 21 mg/dL with vehicle vs 134 ± 7 mg/dL with CP-91149).[38]

Using kinetic experiments, Oikonomakos and colleagues found that the T-state of glycogen phosphorylase b enzyme is the best confirmation to target when looking for glycogen phosphorylase inhibitors.[39] They found CP-320626 to be an inhibitor of the human liver glycogen phosphorylase by binding at the allosteric site compared with the inhibitor site that CP-91149 binds to, which conforms glycogen phosphorylase to its T-state.[39]

The development of glycogen phosphorylase inhibitors is promising; continued research to identify other potential targets of hepatic glucose production is needed.

Glucokinase Activators

Glucokinase is a monomer that resides in the liver and the pancreas. It determines the rate of glucose metabolism by regulating the amount of insulin produced and released from pancreatic beta-cells in response to the amount of glucose in the blood; elevated levels of glucose will increase glucokinase levels in the pancreas, thereby increasing the release of insulin. In addition, glucokinase influences hepatic lipid metabolism and gluconeogenesis in the liver.[40]

Glucokinase has been found to function in patients with type 2 diabetes but to a lesser degree than in individuals without diabetes. The development of a compound that would directly affect glucokinase may help to increase the amount of insulin released in those who have insulin deficiency.

According to Grimsby and colleagues, glucokinase in the pancreas is a glucose sensor, causing insulin to be released once blood glucose levels reach a certain threshold, approximately 5 mM.[41] Glucokinase in the liver is regulated by a glucokinase regulatory protein, which prevents glucokinase from becoming activated and available until glucose must be metabolized, such as after meals, when insulin must be released to normalize blood glucose. In patients with type 2 diabetes, glucokinase in the liver has been found to be reduced by approximately 50%.[42]

Using the kinetic activity of glucokinase, recent studies have shown many glucokinase activators (GKAs), including GKAs 1 through 14, that increase the enzymatic activity of glucokinase. GKAs bind to the allosteric site of glucokinase, which increases the maximum velocity and/or glucose affinity of glucokinase via glucose metabolism.[43] As mentioned earlier, one possible side effect of GKAs is that they can induce moderate hypoglycemia, because they increase the amount of insulin released. This side effect can be reduced by creating a GKA that has less of an impact on the glucose concentration at half the maximum velocity.[43]

As a result of the active role that glucokinase plays in glucose homeostasis and, as a glucose sensor, in the release of insulin to decrease blood glucose levels, the development of a drug that can increase the impact or activity of glucokinase looks promising for treating type 2 diabetes.

G Protein–Coupled Receptor 119 Agonists

G protein–coupled receptor 119 (GPR119) is a long-chain fatty acid receptor that is chiefly expressed by pancreatic beta-cells.[44] The physiologic role of GPR119 remains unknown. Even so, its function has been elucidated through GPR119 agonists that have been shown to couple to $G\alpha_s$.[44] Upon activation by an agonist ligand, GPR119 increases cyclic AMP (cAMP) and induces insulin release. Indirectly, activating GPR119 also stimulates the release of incretins glucagon-like peptide (GLP)-1 and gastric inhibitory peptide. Taken together, GPR119 agonists may act as a potential target for glycemic control in patients with type 2 diabetes through direct insulinotropic effects and indirectly through incretin release.[44]

Using in situ hybridization analysis, Chu and colleagues demonstrated that GPR119 was highly expressed by beta-cell islet population.[44] To determine the significance of GPR119 in glucose homeostasis, the investigators used the highly selective GPR119 agonist AR231453. They found that AR231453 significantly increased cAMP levels in HEK 293 cells, suggesting that GPR119 couples to $G\alpha_s$.[44] Moreover, to demonstrate that AR231453 effectively stimulated GPR119 endogenously, the hamster beta-cell line HIT-T15 expressing GPR119 was used, which in the presence of AR231453 increased cAMP levels.

In addition, the cAMP levels increased in the presence of only a modest amount of glucose, indicating that GPR119 agonists are glucose-dependent for activation.[44] Using a model involving GPR119 beta-cell–expressing mice with type 2 diabetes, the investigators demonstrated a significant improvement in glucose tolerance by enhancement of glucose-dependent insulin release. However, in mice with *GPR119* gene deletion from the X-chromosome, AR231453 had no effect on glucose levels.[44] Surprisingly, Chu and colleagues showed that oral treatment with a GPR119 agonist AR231453 provided better glycemic control than intravenous treatment, which suggests possible incretin involvement.[44]

Adding to these results, Yoshida and colleagues confirmed that the GPR119 agonist AS1907417 is effective in preserving beta-cells and controlling glucose levels in HEK293 cells expressing human GPR119.[45] Furthermore, Flock and colleagues demonstrated that AR231453 not only directly increases insulin, incretin, and GLP-1 levels but also, independently of incretins, slows gastric emptying.[46] Overall, GPR119 agonists, by activating several complementary pathways, may provide a mechanism for glucose control in patients with type 2 diabetes.

Protein Tyrosine Phosphatase 1B Inhibitors

Protein tyrosine phosphatase (PTP) 1B inhibitors may be a possible oral therapeutic target for glycemic control and weight management through sustained insulin and leptin release in patients with type 2 diabetes. PTP1B is part of the protein tyrosine phosphatase family that is found ubiquitously in cells whose function is the removal of a phosphate group from the tyrosine phosphate receptor. In the insulin cascade, a cytosolic protein tyrosine phosphatase negatively controls insulin release by the dephosphorylation of several of the insulin receptor kinase substrates.[47]

In addition, PTP1B inhibitors play a role in downregulation of leptin signaling by dephosphorylating Janus kinase 2 found downstream of the leptin receptor.[48] As a result of its involvement in increasing insulin and leptin sensitivity and improving glucose homeostasis, PTP1B may be an oral therapeutic alternative for patients who have type 2 diabetes with functioning beta-cells.

PTP1B has been shown to be an important part in the insulin and leptin signaling pathway. A study with PTP1B-knockout mice demonstrated resistance to obesity and increased insulin sensitivity.[49] In a recent study in monkeys, inhibition of PTP1B with antisense oligonucleotides led to improved insulin sensitivity.[50] Along with peripheral tissues, neuronal PTP1B has also been implicated in controlling adiposity and leptin sensitivity.[51]

Many PTP1B inhibitors are being manufactured and studied. However, the drawbacks of PTP1B inhibitors include their low affinity to and selectivity for the enzyme and their difficulty with membrane permeability.[48] The catalytic domain contains 2 negative charges, therefore making charged ligands preferred for affinity and selectivity. Charged molecules have decreased membrane permeability. One strategy enlisted to increase membrane permeability has been the addition of a hydrophobic region.[52] More research is needed to determine the best strategy for delivery of the inhibitor to the cytosol and to determine the selectivity of that inhibitor for PTP1B to achieve the most benefit from oral PTP1B inhibitor therapy.

Glucagon-Receptor Antagonists

Glucagon is a peptide hormone secreted by alpha-cells in the pancreas. It raises blood glucose by enhancing glycogenolysis and gluconeogenesis through the activation of cAMP-dependent protein kinase cascade in the liver, and it is the primary counterregulatory hormone to insulin.[53] When excess glucagon is secreted, a process frequently seen in type 2 diabetes, fasting and postprandial hyperglycemia ensues.[54,55]

Accordingly, new therapeutic agents that can block glucagon action could lower fasting and postprandial blood glucose and potentially emerge as a new drug class in the treatment of type 2 diabetes.

Although many glucagon-receptor antagonists have been developed and tested over the past 20 years, only one human study had been published. Bay 27-9955, a nonpeptide compound that competitively blocks the interaction of glucagon with the human glucagon receptor, was tested in 8 normal volunteers in a double-blind, placebo-controlled, crossover study. A single dose of 200 mg was able to block the effect of exogenous glucagon, thereby stabilizing plasma glucose concentrations and the rate of glucose production in the study participants.[56]

The future for this drug class is uncertain, because of the limited published human data currently available. Much more information is needed to elucidate the efficacy and safety of this potential treatment.

Conclusion

Diabetes is a complex and costly disease. Although a cure is not imminent, many treatment options are currently available to aid in the control and management of this disease that is continuing to increase in the United States. However, despite this abundance of therapeutic options, the majority of American patients with type 2 diabetes are not achieving appropriate glycemic control. Novel therapies are in various stages of development, and some are showing promising results in clinical trials. Adding new options with new mechanisms of action to the treatment armamentarium may eventually help improve outcomes and reduce the cost burden of this condition. It is prudent to remain optimistic as the research in this field continues to evolve. ■

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STAKEHOLDER PERSPECTIVE

New Therapies with Novel Mechanisms of Action Are Urgently Needed for Type 2 Diabetes

MEDICAL DIRECTORS: Type 2 diabetes mellitus is currently an area that supports a worldwide "growth industry" in the worst sense of the term. The prevalence of this systemic metabolic disorder continues to rise exponentially as the world's population struggles with ongoing and worsening imbalances between increasing caloric intake and decreasing caloric expenditure, especially in individuals with concomitant insulin resistance.

The consequences of type 2 diabetes are burdensome for all patients with this disease and potentially fatal for a sizable fraction of diabetic patients, because the risks for renal failure, cardiovascular disease, and lower-extremity amputations are dramatically increased in this patient population compared with the age-matched risk in individuals free of diabetes.

DRUG MANUFACTURERS: This epidemic of patients with diabetes has led to a phenomenal proliferation in the number of medications available to treat the disease, with dramatic increases in the number of both oral and injectable preparations. Nevertheless, despite this pharmacologic cornucopia, the majority of patients with type 2 diabetes still do not have their blood glucose levels under adequate control.

Therefore, there remains a significant need for additional classes of medications that can work through novel mechanisms of action to improve the control of blood glucose levels in patients whose levels are not being controlled with currently available medications. The emerging classes of antidiabetic medications discussed in this article by Nguyen and colleagues afford the hope that we may eventually be able to obtain better pharmacologic control of the runaway blood glucose that bedevil so many of our diabetic patients.

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